

## **REMARKS**

### **Status of the Claims**

Claims 76-92, 94-104, and 106-115 are pending in the application. Claims 76-91 and 98-104 are currently withdrawn from consideration. Claims 92, 94-97, and 106-109 stand ready for further action on the merits. Claims 110-115 are added. Support for new claims 110-114 can be found in claims 92 and 107. Support for new claim 115 can be found in the present specification, *inter alia*, at page 16, first paragraph. Thus, no new matter has been added. Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

### **Drawings**

Since no objection has been received, Applicants assume that the drawings are acceptable and that no further action is necessary. Confirmation thereof is respectfully requested.

### **Issues under 35 U.S.C. § 102(b)**

Claims 92, 97, and 106 are rejected under 35 U.S.C. § 102(b) as being anticipated by Finke '090 (CA 2394090). Applicants respectfully traverse. Reconsideration and withdrawal of this rejection are respectfully requested based on the following considerations.

### **Legal Standard for Determining Anticipation**

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis*

*verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

*Distinctions over the Cited Reference*

At page 3 of the outstanding Office Action, the Examiner alleges that Finke '090 anticipates the claimed invention because Finke '090 teaches oligosaccharide mixtures that contain a neutral fraction and an acidic fraction derived from milk and that Finke '090 teaches that lacto-N-neo-tetraose (a neutral oligosaccharide) and 2,3'-sialyl lactose (an acidic oligosaccharide) can be used in such mixtures. However, Finke '090 is silent regarding the fact that each of lacto-N-neo-tetraose and 2,3'-sialyl lactose are specific receptor analogues. Each oligosaccharide is merely one example among many oligosaccharides falling within the broad group of neutral oligosaccharides or the broad group of acidic oligosaccharides present in animal milks.

Thus, Finke '090 selects milk oligosaccharides only on the basis of whether they are acidic or neutral and combines these fractions in ratios that are more similar to the ratio of acidic/neutral oligosaccharides found in human milk. Finke '090 does not consider whether the selected milk oligosaccharides have an effect because they serve as excellent carbon sources for beneficial bacteria because they bind pathogenic bacteria, because they bind potential adhesion sites for the bacteria, or because they stimulate the immune system. Thus, the genus of neutral and acidic oligosaccharides taught by Finke '090 is quite broad.

In *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075 (Fed. Cir. 2008), the Federal Circuit held the following:

However, as the district court recognized, that is not the correct view of the law of anticipation, which requires the specific description as well as enablement of the subject matter at issue. To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); see also, e.g., *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference").

In that same case, the Federal Circuit stated:

The district court analyzed the question as whether a generic disclosure necessarily anticipates everything within the genus, and recognized that the answer depends on the factual aspects of the specific disclosure and the particular products at issue. See, e.g., *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006)...In *In re Ruschig*, 343 F.2d 965, 974 (CCPA 1965), the court declined to find the disclosed genus anticipatory of everything within its scope, when the description of the genus would not lead a person of ordinary skill to a "small recognizable class with common properties."

As the case law above points out, a disclosed genus is not necessarily anticipatory of everything within its scope. The genus of acidic oligosaccharides found in the milk of one or more animals and the genus of neutral oligosaccharides found in the milk of one or more animals are both large. Although particular acidic and neutral oligosaccharides (*i.e.*, lacto-N-neo-tetraose and 2,3'-sialyl lactose) are discussed by Finke '090, Finke '090 does not examine whether the individual oligosaccharides serve any of the functions (*e.g.*, carbon source, receptor analogue, immune system stimulator) discussed above. In fact, some of the oligosaccharides selected by the processes of Finke '090 will likely have no such functions.

The present invention is directed to methods of treating a gastrointestinal infection or preventing such an infection by administering an effective amount of a composition containing purified fractions of at least two compounds containing a pathogen inhibiting oligosaccharide sequence, wherein said oligosaccharide sequence is selected from a defined group of pathogen receptors. Lacto-N-neo-tetraose and 2,3'-sialyl lactose fall within this much narrower group of oligosaccharides that act as pathogen receptors (*e.g.*, receptor analogues). This narrower group obviously includes members from the broad genus of neutral and acidic oligosaccharides disclosed by Finke '090, but this narrower group also excludes many oligosaccharides within the broad genus of neutral and acidic oligosaccharides present in milk that may or may not have other functions that improve the immune response to pathogenic microorganisms.

Based on the teachings of Finke '090, one of ordinary skill in the art would have to blindly pick and choose among all neutral oligosaccharides and all acidic oligosaccharides present in animal milk(s) without knowing which oligosaccharides function as receptor analogues to gastrointestinal infection-causing microorganisms to arrive at the claimed invention.

Moreover, Finke '090 discloses mixing at least two oligosaccharide fractions comprising at least two different oligosaccharides including neutral and/or acidic oligosaccharides to obtain a mixture comprising acidic and neutral saccharides in certain ratio. Furthermore, the term "oligosaccharide" in Finke '090 appears to include glycoproteins or glycolipids and their fragments, making it even more difficult to define the contents of fractions indicated. Since the terms "neutral" and "acidic" are chemically very broad terms, which include heterogeneous groups of glycans with a number of activities, the teaching of Finke '090 is not towards any exact oligosaccharide composition, and the specification of Finke '090 lists only a few rather vague examples of these. Therefore, Finke '090 would lead one of ordinary skill in the art to an indefinite number of saccharide combinations, most of which are likely inactive with regard to any medical indications suggested since not every oligosaccharide has a medical effect as shown by the present invention. The list of indications of Finke '090 is practically everything to which any oligosaccharide substance is known to have affected. Thus, one of ordinary skill in the art would have to:

- 1) produce an infinite number of oligosaccharide compositions comprising acidic and neutral oligosaccharides;

- 2) exclude all possible combinations present in original animal milks, as disclaimed and taught in the specification and claim 1 of Finke '090 (according to claim 1, the total spectrum of the mixture must differ from the same of animal milks); and

- 3) analyze the effect against an endless list of infections and other conditions mentioned.

The teaching of Finke '090 on isolating oligosaccharides from animal milks and the effect of this is unclear because any specific oligosaccharide mixture is the same independently of its origin. Claim 1 of Finke '090 indicates that a disclaimed composition not having the effect of Finke '090 is a composition comprising the glycan components in a natural ratio present in animal milk. However, the natural variations during lactation cause animal milks to contain practically all possible ranges of acidic and neutral oligosaccharides if huge numbers of possible mammalian and marsupial animals producing milk are considered. Therefore, the teaching of Finke '090 is confusing as this disclaimer practically disclaims all compositions isolated from animal milk.

However, the Examiner alleges that Finke '090 teaches such a small number of species (10 possible combinations of disclosed species) that one of ordinary skill in the art could immediately envisage the combinations of those and would end up with a single combination of components based on the separate examples in Finke '090. Applicants respectfully traverse.

First, the disclaimer of Finke '090 excluding original animal milk combinations excludes the combination of individual components of the specific examples, as such composition is realized to be a natural animal milk composition, when considering all possible animals and natural variations of animal milk oligosacchrides. This teaching combined with an infinite functional disclaimer renders it impossible to define any saccharide ratio being definitely taught by Finke '090.

Second, from the examples given in Finke '090, one of ordinary skill in the art can see that components are selected to gain novelty compared to known animal oligosaccharide compositions by selecting rare or non-human glycan compositions or even unknown oligosaccharides. For example, Examples 2 and 4 disclose N-glycolyl-neuraminic acid containing glycans. Example 5 discloses cow disialyl-lactose, two goat isomeric fucosyl-tetrasaccharides, and 3 unknown goat hexasaccharides with specified composition. Because of the disclaimer, it is impossible to know if these are meant to be combinable. According to Finke '090, any combination of these would require knowledge beyond one of ordinary skill in the art. Furthermore, the Applicant of Finke '090 has argued in corresponding US proceedings that the oligosaccharides differ from human milk compositions. Considering the variety of human milk, it is not an easy task to formulate a composition, which certainly differs from any human milk.

Third, one of ordinary skill in the art would find many more species disclosed in the examples of Finke '090, and thus, the number of combinations will be much higher (i.e., more than 300) as discussed below.

In Examples 1-7 of Finke '090, there are 16 (2,3,2,2,3,2,2) oligosaccharide-comprising fractions and three specifically excluded fractions (see Example 4: 2,3- and 2,6- Sialyl-lactoses other than NeuGcα2,3Lactose and NeuGcα2,6Lactose and Example 6: goat larger sialyl oligosaccharides and neutral trisaccharides). These fractions include chemically named components or component groups (other than neutral or acid, which originate from limitedly defined purification processes).

The acidic saccharides listed in the examples of Finke '090 are bovine acid sialyl-oligosaccharides, sheep N-glycolyl neuraminic acid oligosaccharides, goat NeuGc $\alpha$ 2,3Lactose and NeuGc $\alpha$ 2,6Lactose, Cow disialyl-lactose, possible casein acidic O-glycans, and possible lactoferrin acidic N-glycan (acid/neutral status of individual protein were not indicated, nor oligosaccharide production process).

The neutral saccharides listed in the examples of Finke '090 are Sheep oligosaccharides including galactosyl-lactose; 3 isomeric galactosyllactose molecules, fucosylized lactose, GlcNAc-lactose and GalNAc-lactose; lacto-N-neo-tetraose, lacto-N-neo-hexaose, two difucosylated tetrasaccharides from goat; 3 unknown goat hexasaccharides with specified composition, Goat unknown pentasaccharide, possible casein neutral O-glycans, and possible lactoferrin neutral N-glycan (acid/neutral status of individual protein were not indicated, nor oligosaccharide production process).

The excluded components are (1) Acidic: Sialyl2,3Lactose and Sialyl2,6Lactose, goat larger sialyl oligosaccharides and (2) Neutral: neutral trisaccharides of goat.

The number of chemically indicated components, which could be separated from the fractions are:

Acidic: 6 species (included components) and 2 species (excluded) = 8 specified species mentioned + acidic oligosaccharide mixtures containing other components, 7 species, possible product by process (Example 2: sheep, goat and cow mixed whey fractions; Example 3: two fractions possibly acid; Example 4: goat acid mixture; Example 7: acid O-glycan N-glycan mixture. Thus, the total amount of acidic products mentioned is 15 species.

Neutral: 17 species (included) and one composition (excluded) = 18 species mentioned + neutral oligosaccharide mixtures 5 species (Example 1: bovine neutral, Example 4: cow neutral, Example 5: LactoN-neotetra and hexa mixture, mixture of 2 fucotetraoses; Example 6: goat neutral mixture, Example 7: neutral O-glycan N-glycan mixture). Thus, the total number of neutral products mentioned in the examples is 23 species.

There are 16 named compositions, which contain 38 named component species. The number of acid or neutral combinations is thus at least  $15 \times 23 = 345$ . As the teaching of Finke '090 is unclear and may include combining mixed acid and neutral compositions with acid and/or neutral oligosaccharides, the number of binary combinations is actually much higher.

Furthermore, Finke '090 teaches trinary combinations, which increase the combinations into the thousands. Thus, the Examiner has picked one combination of the many disclosed in Finke '090.

Therefore, Finke '090 does not disclose the selection or any specific example of the structurally defined oligosaccharide combinations of the present invention. Accordingly, the present invention is not anticipated by Finke '090 since the reference does not teach or provide for each of the limitations recited in the pending claims.

**Issues under 35 U.S.C. § 103(a)**

Claims 94-96 and 107-109 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Finke '090 in view of Zopf or Pickering et al. (Infection 21 (1993) No. 6, pages 355-357). Applicants respectfully traverse. Reconsideration and withdrawal of this rejection are respectfully requested based on the following considerations.

**Legal Standard for Determining Prima Facie Obviousness**

MPEP 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

*Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See MPEP 2143.03.

Distinctions over the Cited References

At page 4 of the outstanding Office Action, the Examiner concedes that Finke '090 does not teach specific pathogens or their effects. The Examiner relies on the teachings of Zopf and Pickering et al. to overcome this deficiency in the teachings of Finke '090.

Zopf teaches generally that oligosaccharides have been shown to prevent adhesion of certain pathogens to specific tissues. At page 1020, Zopf generalizes that “[c]andidates for prevention and/or therapy of gastrointestinal diseases include soluble forms of carbohydrate receptors [e.g., oligosaccharides] recognized by such pathogens as enterotoxigenic *E. coli*, *V. cholerae*, *Cryptosporidium parvum*, and *H. pylori*.” However, Zopf does not teach what the structures of these soluble carbohydrate receptors are. Although Zopf teaches an oligosaccharide structure that is similar to that of the claimed invention (e.g., Galβ1-4GlcNAcβ1-3Galβ1 at page 1019), Zopf merely states that it “has been proposed as a receptor for adherence of *S. pneumoniae* [causing lung infections] to buccal [cheek] epithelial cells.” Thus, this oligosaccharide structure is not implicated by Zopf in being relevant to pathogens that cause gastrointestinal illnesses.

In the table at page 1017, although Zopf teaches that specific oligosaccharides have been shown to be effective antiadhesive agents for certain organisms (e.g., *E. coli*, *H. pylori*, and *S. typhimurium*) *in vitro* and/or prophylactic or therapeutic *in vivo*, Zopf does not teach what the actual structures of these oligosaccharides are. Further, one of ordinary skill in the art would recognize that *in vitro* studies, while informative, are not necessarily predictive of *in vivo* results. Thus, Zopf does not teach specific oligosaccharide structures useful in combating pathogenic microorganisms that can cause gastrointestinal infections.

Similarly, Pickering et al. also do not teach specific oligosaccharide structures that function as receptor analogues to pathogenic microorganisms that can cause gastrointestinal infections. Pickering et al. merely point out that certain glycoconjugates in human milk have been found to provide protection against enteropathogens in *in vitro* and/or *in vivo* studies without specifying specific structures or indicating which pathogens had been studied *in vitro* and which *in vivo*.

At page 5 of the outstanding Office Action, the Examiner asserts, “It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer Finke’s composition to a subject suffering from or at risk for bacterial infections such as those taught by Zopf or Pickering. Finke teaches the treatment of bacterial gastrointestinal infections generally, and



Zopf and Pickering teach particular bacteria which are known to be treatable using oligosaccharides. Thus, the skilled artisan could predict that the bacterial infections taught by Zopf or Pickering could be treated using Finke's oligosaccharide composition."

MPEP 2144.08 states:

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck & Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

The same section of the MPEP states that under such circumstances, the Examiner must determine whether one of ordinary skill in the art would have been motivated to select the claimed species (*i.e.*, lacto-N-neo-tetraose and 2,3'-sialyl lactose) from a prior art genus. None of Finke '090, Zopf, and Pickering et al. teach the specific structures of oligosaccharides that have antiadhesive properties in relation to pathogens that cause gastrointestinal infections as in the claimed invention. Thus, the teachings of Zopf and Pickering et al. would not aid one of ordinary skill in the art in choosing from among the broad genus of acidic and neutral oligosaccharides derived from milk taught by Finke '090 to arrive at the claimed invention.

In fact, Zopf and Pickering et al. do not add a great deal beyond Finke '090 that some oligosaccharides can act as receptor analogs for certain pathogens, other than suggesting specific pathogens that may be inhibited in their ability to adhere to certain tissues or protected against with oligosaccharides. Zopf and Pickering et al. give no guidance as to which oligosaccharide structures are effective to treat or prevent gastrointestinal infections.

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be disclosed by the cited references. As discussed above, Finke '090 in view of Zopf or Pickering et al. fail to disclose all of the claim limitations of independent claim 92, and those claims dependent thereon. Accordingly, the combinations of references do not render the present invention obvious.

Furthermore, the cited references or the knowledge in the art provide no reason or rationale that would allow one of ordinary skill in the art to arrive at the present invention as claimed. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejection is respectfully requested. Any contentions of the USPTO to the contrary must be reconsidered at present.

#### **New Claims 110-115**

Applicants have newly added claims 110-115 in an effort to further define the scope of protection owed to Applicants. Applicants respectfully submit that claims 110-115 are allowable for the reasons given above. As such, Applicants respectfully assert that claims 110-115 clearly define over the cited references, and an early action to this effect is earnestly solicited.

#### **Conclusion**

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Chad M. Rink, Registration No. 58,258, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: September 20, 2010

Respectfully submitted,

By 

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